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Stereoselective reduction of *N*-hydroxy-α-iminocarbonyl-oligopeptide methyl esters with Zn–MsOH

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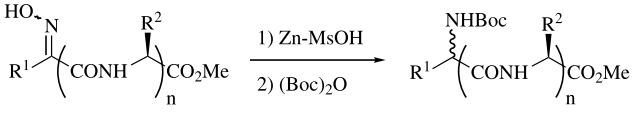
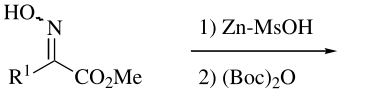
Abstract—The reduction of *N*-hydroxy-α-imino esters with Zn–MsOH in THF afforded α-amino esters in high yields. The reduction of *N*-hydroxy-α-iminocarbonyl-oligopeptide methyl esters prepared from L-phenylalanine and L-leucine di-, tri-, tetrapeptides gave the corresponding *S*-formed oligopeptide methyl esters in moderate diastereoselectivities.

Reduction of oximes is a useful method for the synthesis of amines from carbonyl compounds.[1] Recently, we have reported the reductive coupling of aromatic aldoximes and azines to *N*,*N*′-unsubstituted 1,2-diamines with Zn–MsOH or Zn–$TiCl_4$.[2,3] We found that the reduction with Zn–MsOH was also effective for the conversion of *N*-hydroxy-α-imino esters to α-amino esters. We further investigated the reduction of *N*-hydroxy-α-imino carbonyl groups bonded to the N-terminus of L-phenylalanine or L-leucine oligopeptides with Zn–MsOH (Eq. (1)). Herein we report that the diastereoselectivity in the reduction of *N*-hydroxy-α-iminocarbonyl-oligopeptide methyl esters was strongly affected by the number of amino acid residues of the oligopeptide moieties. The *S*-selectivity increased with increase in the number of amino acid residues (*n*) in the substrates, *N*-hydroxy-α-iminocarbonyl-(L-Phe)$_n$-OMe and *N*-hydroxy-α-iminocarbonyl-(L-Leu)$_n$-OMe ($n=1$–4).



R^1 = Me, Bn, *i*-Bu; R^2 = Bn, *i*-Bu; n = 1-4 (1)

First, the reduction of *N*-hydroxy-α-imino esters was carried out with Zn–MsOH in THF at 25°C. After *N*-Boc-protection of the resulting α-amino esters, *N*-Boc-α-amino esters were obtained in excellent yields (Eq. (2)). In order to complete the reduction, the addition of MsOH in amounts equimolar with Zn was required. These results show that Zn–MsOH is an effective reducing agent for the reduction of *N*-hydroxy-α-imino esters to α-amino esters.



R^1 = Me, 87%
R^1 = Bn, 88%
R^1 = *i*-Bu, 90% (2)

Second, a series of *N*-hydroxy-α-iminocarbonyl-oligopeptide methyl esters **1a–d** (R^1 = Me) and **1e–h** (R^1 = Bn) prepared from L-phenylalanine methyl ester ($n=1$) and L-phenylalanine oligopeptide methyl esters ($n=2$–4) were reduced with Zn–MsOH in THF or DMF at 25°C. The results are summarized in Table 1. In all cases, *N*-Boc-oligopeptide methyl esters **2** were obtained as mixtures of two diastereomers ((*S*)-**2** and (*R*)-**2**) in good to excellent yields. The *S*:*R* ratios at the N-terminal residues in **2** were determined by comparison of their ^{1}H NMR spectra with those of authentic samples.[4] Fig. 1 illustrates the correlation between the percentage of the *S*-form in **2** and the number of amino acid residues (*n*). In THF, the *S*-selectivity rose steadily with an increase of the number of residues. Whereas slight *R*-selectivities were found in the reduction of the substrates **1a** and **1e** derived from L-phenylalanine

Keywords: reduction; zinc; oxime; amino acid; oligopeptide.

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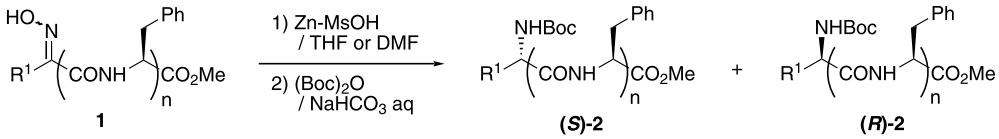
Table 1. Reduction of *N*-hydroxy-α-iminocarbonyl-oigopeptide methyl esters **1** with Zn–MsOH



			In THF					In DMF		
1	R^1	*n*		Yield[a] (%) of **2**	*S*:*R*[b]	1	R^1	*n*		Yield[a] (%) of **2**	*S*:*R*[b]
1a	Me	1	**2a**	91	45:55	**1a**	Me	1	**2a**	89	41:59
1b	Me	2	**2b**	85	68:32	**1b**	Me	2	**2b**	87	55:45
1c	Me	3	**2c**	77	75:25	**1c**	Me	3	**2c**	78	60:40
1d	Me	4	**2d**	71	85:15	**1d**	Me	4	**2d**	75	60:40
1e	Bn	1	**2e**	92	48:52	**1e**	Bn	1	**2e**	87	42:58
1f	Bn	2	**2f**	89	63:37	**1f**	Bn	2	**2f**	88	44:56
1g	Bn	3	**2g**	83	70:30	**1g**	Bn	3	**2g**	85	46:54
1h	Bn	4	**2h**	77	82:18	**1h**	Bn	4	**2h**	66	42:58

[a] Isolated yields.
[b] Determined by ^{1}H NMR spectra.

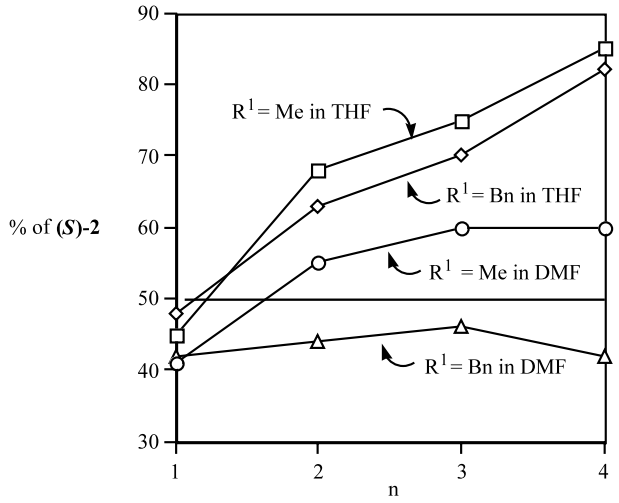
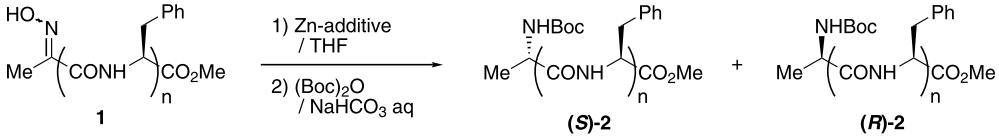


Figure 1. Correlation between percentage of (*S*)-**2** and number of residues (*n*).

methyl ester ($n=1$), *S*-formed diastereomers of **2** were obtained preferentially from the substrates **1b–d** and **1f–h** made of L-phenylalanine di-, tri-, and tetrapeptides methyl esters ($n=2$–4). Unfortunately, the substrate prepared from a pentapeptide methyl ester ($n=5$) was sparingly soluble in THF. On the other hand, when the reduction of **1** was carried out in DMF, the stereoselectivities were relatively low (40–60% of *S*-**2**). Especially, in the cases of $R^1=$Bn (**1f–h**), the selectivity remained stable at 40–45% of the *S*-form. Next, TFA and $TiCl_4$ were used as an additive in place of MsOH. As depicted in Table 2, the yields of **2** were slightly less than those obtained with Zn–MsOH. As to the diastereoselectivity in **2**, Zn–TFA gave similar results to those with Zn–MsOH, while Zn–$TiCl_4$ afforded considerably low *S*-stereoselectivities.

Another series of substrates **3a–d** ($R^1=$Me) and **3e–h** ($R^1=i$-Bu) derived from L-leucine methyl ester ($n=1$) and oligopeptide methyl esters ($n=2$–4) were also

Table 2. Reduction of **1a–d** with Zn–TFA or Zn–$TiCl_4$ in THF



		With Zn–TFA				With Zn–$TiCl_4$			
1	*n*		Yield[a] (%) of **2**	*S*:*R*[b]	**1**	*n*		Yield[a] (%) of **2**	*S*:*R*[b]
1a	1	**2a**	66	40:60	**1a**	1	**2a**	71	44:56
1b	2	**2b**	63	67:33	**1b**	2	**2b**	69	40:60
1c	3	**2c**	61	70:30	**1c**	3	**2c**	65	49:51
1d	4	**2d**	55	76:24	**1d**	4	**2d**	48	46:54

[a] Isolated yields
[b] Determined by ^{1}H NMR spectra.

reduced with Zn–MsOH in THF at 25°C as exhibited in Table 3. Fig. 2 represents the correlation between the % of the *S*-form in **4** and *n*. Similarly to the reduction of **1**, the *S*-forms of **4** were obtained selectively from the substrates **3b–d** and **3f–h** ($n=2$–4). However, the *S*-selectivity in **4** rose rapidly from $n=1$ to $n=2$ and leveled off practically at $n=2$.

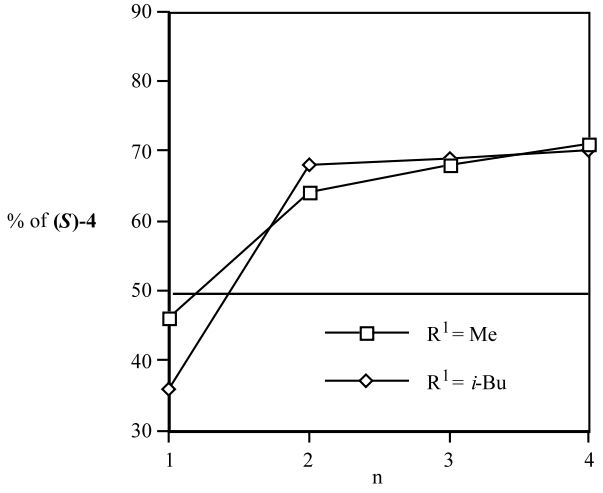
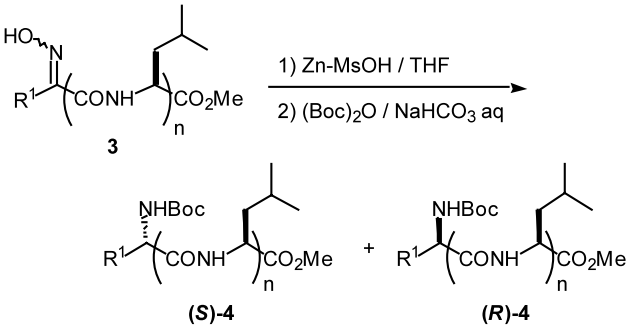


Figure 2. Correlation between percentage of (*S*)-**4** and number of residues (*n*).

As another reducing agent, $NaBH_4$–$CoCl_2{\cdot}6H_2O$[5] was employed for the reduction of **1** (Table 4). In contrast to the results obtained with Zn–MsOH, the diastereoselectivities in **2** were very low irrespective of the number of residues.

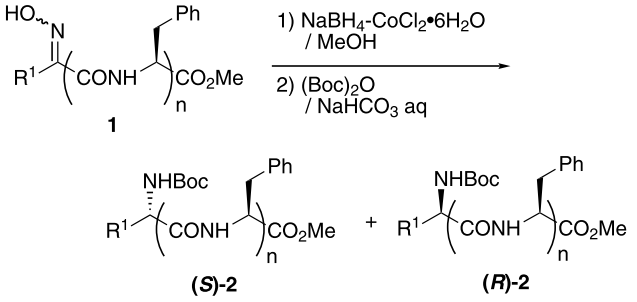
Table 3. Reduction of *N*-hydroxy-α-iminocarbonyl-oligopeptide methyl esters **3** with Zn–MsOH in THF



3	R^1	*n*		Yield[a] (%) of **4**	*S*:*R*[b]
3a	Me	1	**4a**	95	46:54
3b	Me	2	**4b**	85	64:36
3c	Me	3	**4c**	87	68:32
3d	Me	4	**4d**	74	71:29
3e	*i*-Bu	1	**4e**	93	36:64
3f	*i*-Bu	2	**4f**	92	68:32
3g	*i*-Bu	3	**4g**	82	69:32
3h	*i*-Bu	4	**4h**	80	70:30

[a] Isolated yields.
[b] Determined by ^{1}H NMR spectra.

Table 4. Reduction of **1** with $NaBH_4$–$CoCl_2{\cdot}6H_2O$



1	R^1	*n*		Yield[a] (%) of **2**	*S*:*R*[b]
1a	Me	1	**2a**	63	53:47
1b	Me	2	**2b**	80	49:51
1c	Me	3	**2c**	62	45:55
1d	Me	4	**2d**	55	45:55
1e	Bn	1	**2e**	66	46:54
1f	Bn	2	**2f**	77	50:50
1g	Bn	3	**2g**	82	51:49
1h	Bn	4	**2h**	59	46:54

[a] Isolated yields.
[b] Determined by ^{1}H NMR spectra.

In conclusion, the reduction of *N*-hydroxy-α-imino esters and *N*-hydroxy-α-iminocarbonyl-oligopeptide methyl esters with Zn–MsOH in THF gave effectively the corresponding α-amino esters and oligopeptide methyl esters, respectively. The diastereoselectivity in the reduction of *N*-hydroxy-α-iminocarbonyl-oligopeptide methyl esters was not influenced largely by the substituents in *N*-hydroxy-α-iminocarbonyl groups (R^1) and oligopeptides (R^2), but much affected by the number of residues in oligopeptides (*n*). Moderate *S*-selectivities were observed in the reduction of the substrates derived from L-phenylalanine and L-leucine di-, tri-, tetrapeptides ($n=2$–4).

General procedure is as follows: zinc powder (Wako Pure Chemical Industries, Ltd.) was washed with 1 M HCl, water, and ether successively and dried in vacuo. To a solution of *N*-hydroxy-α-iminocarbonyl-oligopeptide methyl ester **1** or **3** (1 mmol) in dry THF (5 mL for $n=1$ and 2, 10 mL for $n=3$, 20 mL for $n=4$) was added freshly distilled MsOH (0.65 mL, 10 mmol) and zinc powder (0.65 g, 10 mmol) at 0°C under an atmosphere of nitrogen. The mixture was allowed to warm to 25°C and stirred for 8 h. To the mixture was added satd $NaHCO_3$ in water (20 mL) and $(Boc)_2O$ (0.44 g, 2 mmol). The mixture was stirred for 1 h at 25°C, filtered, extracted with ethyl acetate. After removal of the solvent, *N*-Boc-oligopeptide methyl ester **2** was isolated as a diastereomeric mixture by column chromatography on silica gel (hexane/ethyl acetate).

Acknowledgements

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4. The chemical shifts (δ) of methyl protons (doublet, $J=7.0$–7.3 Hz) at the N-terminal alanine residues in **2a**–**d** and **4a**–**d** were as follows: (*S*)-**2a** 1.31; (*R*)-**2a** 1.29; (*S*)-**2b** 1.25; (*R*)-**2b** 1.21; (*S*)-**2c** 1.21; (*R*)-**2c** 1.18; (*S*)-**2d** 1.20; (*R*)-**2d** 1.16; (*S*)-**4a** 1.355; (*R*)-**4a** 1.364; (*S*)-**4b** 1.33; (*R*)-**4b** 1.35; (*S*)-**4c** 1.31; (*R*)-**4c** 1.34; (*S*)-**4d** 1.32; (*R*)-**4d** 1.33. The chemical shifts (δ) of Boc protons (singlet) in **2e**–**h** and **4e**–**h** were as follows: (*S*)-**2e** 1.40; (*R*)-**2e** 1.38; (*S*)-**2f** 1.37; (*R*)-**2f** 1.39; (*S*)-**2g** 1.34; (*R*)-**2g** 1.39; (*S*)-**2h** 1.30; (*R*)-**2h** 1.34; (*S*)-**4e** 1.44; (*R*)-**4e** 1.45; (*S*)-**4f** 1.44; (*R*)-**4f** 1.44; (*S*)-**4g** 1.45; (*R*)-**4g** 1.43; (*S*)-**4h** 1.47; (*R*)-**4h** 1.43. The chemical shifts (δ) of methoxy protons (singlet) in **4f** were as follows: (*S*)-**4f** 3.722; (*R*)-**4f** 3.716.
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